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A Novel Mechanism for Benign Essential Blepharospasm

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Purpose: The purpose of this study is to test the hypothesis that the photophobia of benign essential blepharospasm (BEB) is caused by sympathetically maintained pain.

Methods: Nineteen patients with photophobia and BEB were enrolled in an unblinded prospective treatment trial. The intervention was blockade of the superior sympathetic ganglion with local anesthetic. Outcome measures included the patient's subjective report of ocular surface dryness, foreign body sensation, and eyelid spasm. We also obtained video recordings of eyelid movements.

Results: Of the 19 patients, 13 reported subjective improvement in BEB symptoms after cervical sympathetic blockade (CSB). Thirteen of 19 patients also had objective evidence of decreased light-induced eyelid spasm after CSB. Ocular surface disease was present in 18 of 19 patients.

Conclusion: These data support the hypothesis that in many patients with BEB there is a sympathetically maintained pain syndrome associated with external ocular disease. We speculate on a neurologic circuit that may explain these findings.

Benign essential blepharospasm (BEB) is a form of focal dystonia whose cause is obscure. BEB may occur in diseases of the basal ganglia or in association with upper brainstem lesions (1–3). In most patients, however, BEB is idiopathic.

Most published reports have focused on the motor signs of BEB, namely, involuntary contractions of the orbicularis oculi. Treatment for BEB is directed against the involuntary movements; botulinum toxin, myectomy, and neurectomy reduce the force of contraction of the orbicularis oculi.

BEB also has sensory symptoms. In a recent survey, 79% of 1,653 patients with BEB said that bright lights worsen their symptoms of eyelid squeezing (4). In most large series the majority of patients present with sensory complaints of photophobia or ocular irritation that precedes or occurs simultaneously with the development of eyelid spasms (1,5,6). Many BEB patients wear sunglasses even on cloudy days and report that daylight produces ocular discomfort. Little attention has been given to photophobia, which is the most significant sensory component of BEB.

This report investigates the relationship between the sensory and motor components of BEB and elaborates a novel mechanism involving the cervical sympathetic chain. We propose that the sensory component of BEB is a form of sympathetically maintained pain.

The sympathetic nervous system has been implicated in the maintenance of a number of chronic pain syndromes. Collectively these chronic pain syndromes are termed sympathetically maintained

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pain. Cervical sympathetic blockade (CSB) with local anesthetic agents has been found to be effective treatment for some sympathetically maintained pain syndromes, of which reflex sympathetic dystrophy (RSD) is the best characterized (7). RSD is a chronic pain disorder that most often affects the upper extremity. It is thought to be caused by a reverberating neurologic positive feedback loop containing overactive spinal interneurons that stimulate the cervical sympathetic chain, resulting in sensitization of peripheral nocioceptors (8). Such sensitization results in allodynia (pain to light touch).

Many similarities exist between patients with RSD and BEB. In both disorders patients may suffer from dystonic movements. Some patients with RSD have involuntary movements of the affected limb whereas patients with BEB have involuntary eyelid closure. In both disorders patients report non-noxious sensory stimuli as being noxious. Patients with BEB report that daylight produces photophobia; patients with RSD report pain with light touch. It has been suggested that photophobia is a misnomer; photooculodynia should be preferred since normal levels of illumination produce pain. In both disorders patients have abnormalities of exocrine secretion. RSD patients have abnormal sweating and many BEB patients have dry eyes. RSD and BEB patients describe the quality of the pain/photo-oculodyria as burning, with pain typically out of proportion to discernible tissue damage or inflammation. In both disorders symptoms are worsened by exposure to bright light and strong emotions (9).

The similarities between RSD and BEB led us to hypothesize that BEB may be a sympathetically maintained pain disorder. In this study we test this hypothesis by evaluating the effect of CSB on the signs and symptoms of BEB.

METHODS

Nineteen patients with BEB and prominent symptoms of light sensitivity were enrolled. The study was done under the supervision of the Institutional Review Board at the University of Utah.

A thorough history and physical examination was performed to identify potential contraindications to CSB. An ophthalmic history and physical examination was performed to evaluate external eye disease. Additional baseline information was gathered by questionnaire. Before CSB each patient completed visual analog scales ranking global blepharospasm symptoms, severity of light sensitivity, spasm of eyelids, dryness of the eyes, and foreign body sensation on a scale from 0 to 10—0 was defined as "no symptoms" and 10 as "the worst symptoms possible." Baseline tear break-up time and Schirmer test without anesthesia at 10 minutes were obtained. A video recording was made to evaluate eyelid spasm with and without a standard light stimulus.

Patients received sequential bilateral CSB administered by one of the authors (M.G.) as the vital signs were monitored. The blocks were given with a 22-gauge B-bevel needle inserted just lateral to the cricoid cartilage and advanced to the tubercle of C6. After negative aspiration, a 0.25-ml test dose of 1% lidocaine was administered followed by 9.75 ml of 1% lidocaine. Typically, we proceeded directly to block the second side, but if the patient developed a recurrent laryngeal nerve block with the first injection we waited for the laryngeal nerve to recover before proceeding to the contralateral side. Success of orbital sympatholysis was determined by the presence of transient ptosis, miosis, and conjunctival erythema. Conjunctival erythema was the most reliable indicator of sympatholysis.

One hour after block, tear production was measured and the video recording was repeated. Patients scored the visual analog scale 1 hour, 24 hours, and 72 hours after CSB. The video recordings were analyzed in 2-minute segments to determine the fraction of time the eyes were open. One observation was made each second as to whether the eyelids were opened or closed. An open eyelid was defined as having a palpebral fissure width greater than 50% of the maximal palpebral fissure width observed during the 2-minute segment. One hundred twenty observations were made before the light stimulus was turned on, and 120 observations were made after the light stimulus was turned on. These observations were compared with observations recorded before CSB. Statistical significance of all data was determined with the Student t-test.

RESULTS

The subjective data recorded on the visual analogue scales are shown in Figure 1. Before receiving CSB patients reported photophobia as the most bothersome symptom. This was confirmed on a separate questionnaire where patients ranked the fraction of their blepharospasm symptoms caused

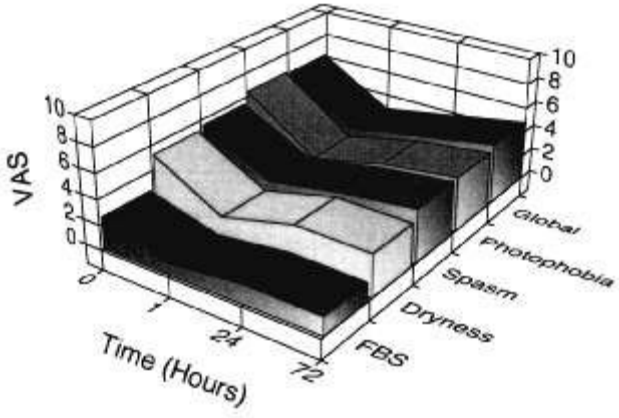

FIG. 1. Visual analogue scales (VAS) before, and 1, 24, and 72 hours after cervical sympathetic block; mean for 19 patients. Values at 1, 24, and 72 hours are significantly less than before block for all symptoms except foreign body sensation where statistical significance was noted at the 1 hour time point ($p < 0.05$, paired Student *t*-test).

by photophobia (37%), eyelid squeezing (30%), dry eye (18%), and foreign body sensation (15%). Figure 1 demonstrates that CSB gave patients relief from BEB symptoms. Relief of photophobia was most marked. The greatest improvement in symptoms occurred 1 hour after block but continued for longer than 72 hours after block. Three of 19 patients reported a rebound phenomenon with symptoms 7 to 14 days after block actually worse than before.

We also analyzed the video recordings of eyelid movements; the results are summarized in Figures 2 and 3. Figure 2 demonstrates that 7 of 19 patients had a significant increase in the fraction of time the eyelids remained open in ambient room light after CSB. Figure 3 demonstrates that in the presence of a standard light stimulus the amount of time eyes remain open is significantly increased by CSB in 13 of 19 patients.

Histograms of Schirmer tests and tear break-up times are given in Figures 4 and 5, respectively. These data demonstrate that an unstable tear film and moderate-to-severe dry eye are common among patients with BEB. Furthermore, 10 of 19 patients had punctate keratitis in at least one eye. Only one of 19 patients had a normal external ocular examination as determined by Schirmer test, tear break-up time, and punctate keratitis.

DISCUSSION

This study supports a role for the cervical sympathetic chain in the maintenance of BEB. Patients experienced subjective improvement in BEB symptoms immediately after block and relief of symptoms in most patients for at least three days (Fig. 1). Patients reported greatest relief from photophobia. This study documents that patients with BEB have photophobia, which is as severe a symptom as eyelid squeezing. We document that exposure to light significantly increased eyelid spasm (Figs. 2 and 3). We also demonstrate that CSB decreased eyelid spasm and that this decrease is most marked during stimulation with light. Five of the 6 patients who failed to respond to CSB also failed to demonstrate light-induced eyelid spasm before CSB. These data suggest that patients who demonstrate significant eyelid spasm with light stimulus are more likely to respond to CSB.

In agreement with previous studies (6,10), we document a 95% incidence of ocular surface disease including abnormal Schirmer test, tear break-up time, and punctate keratitis.

Possible mechanisms for reduced symptoms after CSB include the following. First, CSB creates a transient Horner syndrome with miosis and ptosis, and could reduce the amount of light striking the retina and alleviate photophobia. However, we waited at least 1 hour after CSB before making any measurements and by that time the ptosis and miosis had resolved. In addition to being transient, Horner syndrome was only present in ambient room light. With the light stimulus on, patients squinted and decreased the palpebral fissure width. Squinting was markedly reduced by CSB. The end result was that with the light stimulus on, the pal-

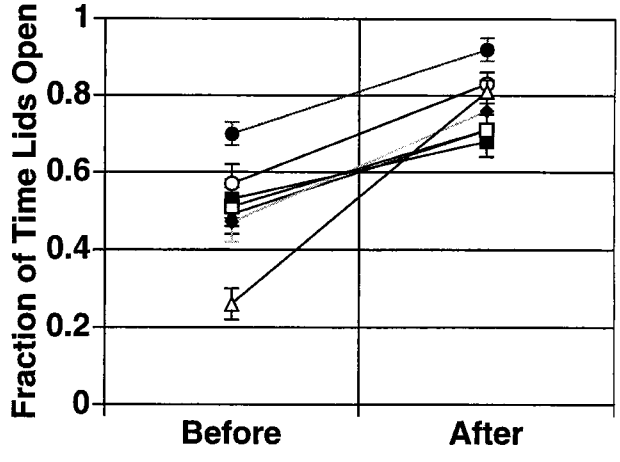

FIG. 2. Percent of the time eyelids are open in ambient room light before and 1 hour after cervical sympathetic block. Data are displayed as mean and standard error for the 7/19 patients who had a significant increase ($p < 0.05$, unpaired Student *t*-test).

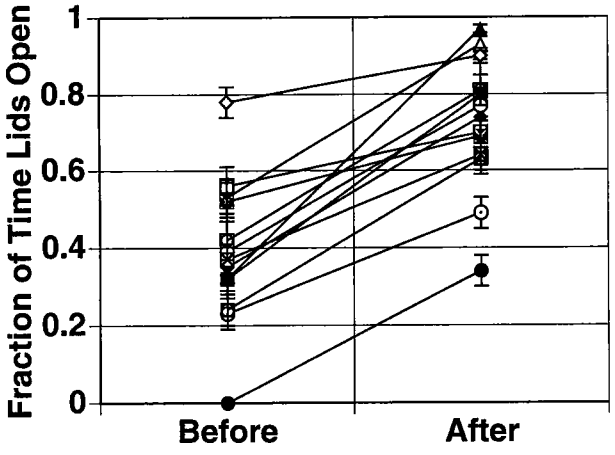

FIG. 3. Percent of time eyelids are open with light stimulus before and 1 hour after cervical sympathetic block. Data are displayed as mean and standard error for the 13/19 patients who had a significant increase ($p < 0.05$, unpaired Student *t*-test).

pebral fissure width is actually greater after CSB than before CSB. The anisocoria of Horner syndrome is greatest in the dark (11). In fact, we were unable to measure any difference in pupillary aperture before and after CSB with the light stimulus on. Horner syndrome was not measurable at any time with the light stimulus on, or even in ambient room light 1 hour after block, so it does not account for the reduction of eyelid spasm seen with CSB.

Another possible explanation for the affects of CSB on BEB is that systemic absorption of lidocaine could cause resolution of symptoms (12). We conclude that this is unlikely because several patients reported that unilateral block resulted in ipsilateral relief of photophobia, consistent with a regional rather than systemic effect of lidocaine injection.

The final confounding variable is the placebo effect. We did not control for the placebo effect due to ethical concerns given the invasive nature of the procedure. Designing a large placebo controlled trial of CSB would be difficult. In a pilot study CSB decreased ocular discomfort in blepharospasm patients with a symptom complex called the photo-oculodynia syndrome (13). A placebo effect was not demonstrated in this study but the small sample size precluded statistical analysis.

The greatest effect of CSB in this study was relief of photophobia. We speculate that the reduction in eyelid squeezing after CSB resulted from a reduction in nociceptive input (Fig. 6). The neurologic connections diagrammed in Figure 6 are the simplest circuit that explains the clinical observations. Many of the brainstem pathways drawn as a single box are probably polysynaptic.

The circuit diagrammed in Figure 6 is inferred from empirical observations about photophobia. Photophobia is an unusual sensory phenomenon that integrates sensory input from the trigeminal and optic nerves. In the proposed neurologic circuit cranial nerves II and V contribute to produce photophobia. Excitation of the optic nerve results in increased sympathetic outflow via a brainstem reflex. This increased sympathetic outflow results in sensitization of nocioceptors, which carry information to the brainstem via cranial nerve V.

Sensitization of nocioceptors by inputs from the sympathetic nervous system has been documented in other organ systems and has been postulated to play a role in sympathetically maintained pain syndromes including postherpetic neuralgia (8,14–18). However, this study is the first to suggest that the cervical sympathetic chain is part of the pathway that produces photophobia in BEB. Suggestive evidence supporting involvement of the sympathetic nervous system in the photophobia experienced in BEB includes anatomic studies that have demon-

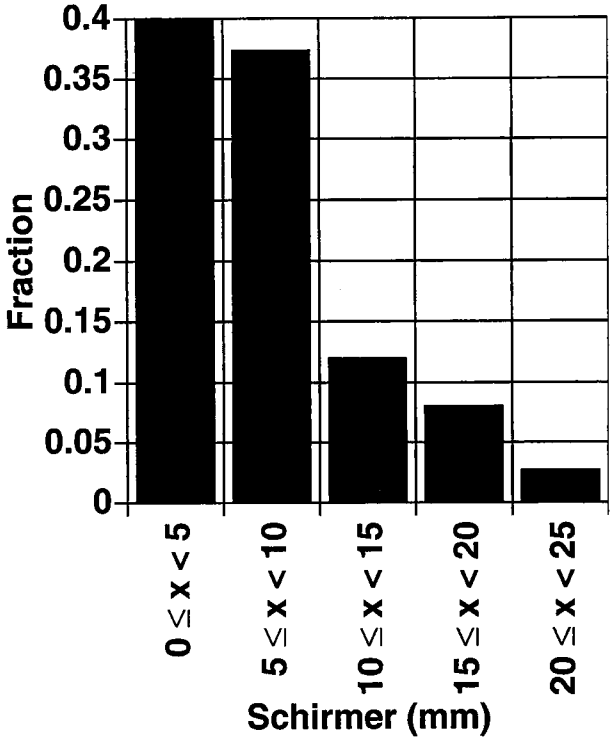

FIG. 4. Histogram demonstrating the distribution of Schirmer test for 38 eyes of 19 patients. Cervical sympathetic block had no significant effect on Schirmer test so data before and after block are combined.

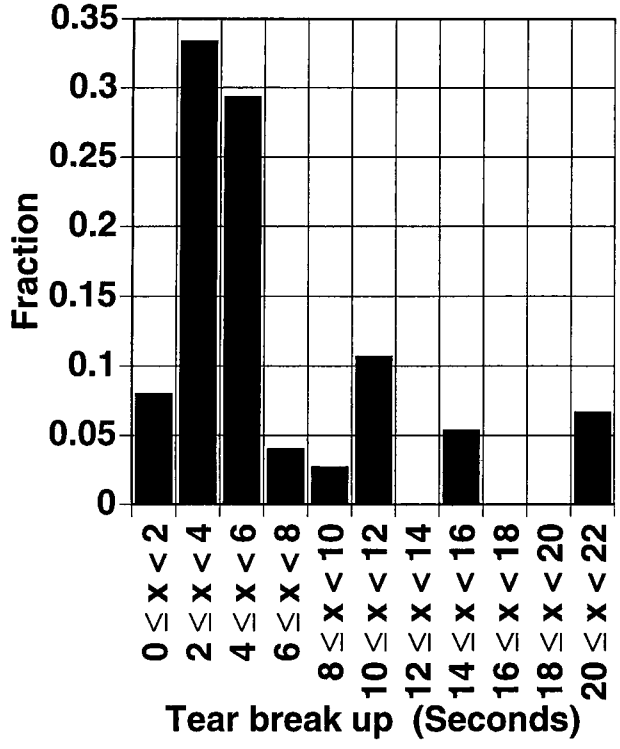

FIG. 5. Histogram demonstrating the distribution of tear break-up times for 38 eyes of 19 patients. Cervical sympathetic block had no significant effect on the tear break-up time so data before and after block are combined.

strated an intimate association of orbital sympathetic nerves with the branches of the ophthalmic division of the trigeminal nerve (19). It also has been demonstrated that mental stress, a stimulus known to worsen symptoms of blepharospasm, results in a marked increase in the rate of firing of the sympathetic nerves that are associated with the supraorbital nerve (20).

Another pertinent historical observation relates to a pain state brought on by surgical sympathectomy. There is a transient condition, sometimes called sympathalgia, of continual pain two to 12 weeks after surgical sympathectomy (9). This is postulated to be caused by denervation hypersensitivity in adjacent areas with incomplete sympathectomy and a focal increase in sympathetic activity. When the sympathectomy includes the stellate ganglion, the eye is mainly affected and the pain has been described as photophobia (21). An association between BEB and the chronic abuse of nasal decongestants containing a combination of sympathomimetic and an antihistamine has been reported (22).

The mechanistic pathway diagrammed in Figure 6 also incorporates the blink reflex whereby noxious corneal stimuli cause contraction of the orbicularis oculi via a brainstem reflex. Corneal touch stimulates external nocioceptors and the signal is relayed from cranial nerve V to VII via brainstem interneurons. Several reports have shown that the brainstem interneurons that modulate the blink reflex are hyperexcitable in patients with BEB (23–27). Interestingly, the postulated cause of sympathetically maintained pain is also hyperexcitability of central nervous system interneurons (8).

Based upon reported laboratory studies (23–27) it is reasonable to propose that BEB is caused by hyperexcitable brainstem interneurons. Figure 6 depicts hyperexcitable brainstem interneurons that supply the gain needed to produce a positive feedback loop involving ocular nocioceptors, the trigeminal nerve, brainstem interneurons, and the cervical sympathetic chain. This reverberating positive feedback loop would result in chronic photophobia and reflex blinking. Shutting down the positive feedback loop with CSB presumably allows the brainstem interneurons to temporarily reset to a less excitable state. This would explain why the beneficial effect of CSB on BEB persisted beyond the pharmacologic duration of action of lidocaine. A dissociation between local anesthetic duration of action and duration of pain relief is commonly observed in patients with sympathetically maintained pain.

We report a very high incidence of ocular surface disease in the group of BEB patients we studied (Figs. 4 and 5). It is tempting to suggest that

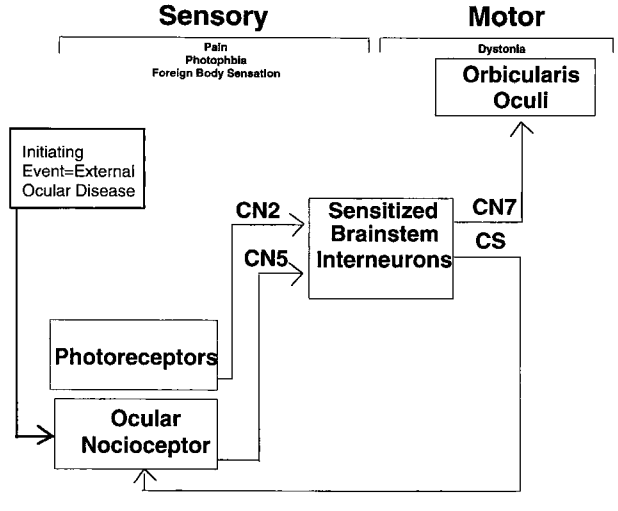

FIG. 6. Speculative neurologic circuit; optic nerve (CN2), ophthalmic division of cranial nerve 5 (CN5), facial nerve (CN7), and the cervical sympathetic chain (CS).

these patients' photophobia and blepharospasm are simply reflex responses to ocular surface disease. However, this is doubtful because application of topical corneal anesthetic did not alleviate patients' symptoms as one sees in the blepharospasm and photophobia associated with a corneal abrasion (authors' unpublished observation). Although it has been suggested that chronic ocular surface disease can trigger BEB in certain patients who have an underlying disorder of hyperexcitable brainstem interneurons (6), we suggest that the reverberating positive feedback loop diagrammed in Figure 6 is the mechanism by which chronic ocular surface disease triggers BEB in predisposed patients. Presumably, chronic excitation of corneal nocioceptors results in a change in the brainstem interneurons that facilitate the blink reflex and the proposed reflex involving the cervical sympathetic chain.

This study proposes a rational mechanism for BEB. We do not imply that CSB is a first-line treatment for BEB. Our data demonstrate short-term improvement of symptoms after an invasive and moderately costly procedure. Although some patients with sympathetically maintained pain receive long-term relief of symptoms from a series of sympathetic blocks, it remains to be determined in a clinical trial if patients with BEB also could receive long-term remission of photophobia and eyelid squeezing symptoms from a series of CSBs.

For BEB patients who, for one reason or another, cannot tolerate CSB as a diagnostic test for the role of the sympathetic nervous system in maintaining the disorder, a systemic alpha-adrenergic blocking drug, phentolamine, could be employed (16). We speculate that a subset of patients with incapacitating BEB may even respond to surgical sympathectomy (28).

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